Short-term fully closed-loop insulin delivery using faster insulin aspart compared to standard insulin aspart in type 2 diabetes

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ABSTRACT

We evaluated the efficacy and safety of short-term fully closed-loop insulin delivery using faster versus standard insulin aspart in type 2 diabetes. Fifteen adults with insulin-treated type 2 diabetes underwent 22 hours of closed-loop insulin delivery with either faster or standard insulin aspart in a double-blind randomised crossover design. Basal-bolus regimen was replaced by model predictive control algorithm-directed insulin delivery based on sensor glucose levels. The primary outcome was time with plasma glucose in target range (5.6-10.0mmol/l) and did not differ between treatments (mean difference [95%CI] -3.3% [8.2;1.7], p=0.17). Mean glucose and glucose variability were comparable, as was time spent below and above target range. Hypoglycaemia (<3.5mmol/l) occurred once with faster insulin aspart and twice with standard insulin aspart. Mean total insulin dose was higher with faster insulin aspart (mean difference [95%CI] 3.7U [0.7;6.8], p=0.021). No episodes of severe hypoglycaemia or other serious adverse events occurred. In conclusion, short-term fully closed-loop in type 2 diabetes may require higher dose of faster insulin aspart compared to standard insulin aspart to achieve comparable glucose control.

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INTRODUCTION

Faster insulin aspart is a novel formulation of conventional insulin aspart that includes niacinamide for quicker absorption following subcutaneous administration[1], resulting in faster pharmacokinetic and pharmacodynamic profiles[2-4]. It was developed to more closely match physiological insulin profile with the goal of improving postprandial glucose control.

The more favourable pharmacokinetic and pharmacodynamic properties of faster insulin aspart compared to standard insulin aspart were substantiated in clinical studies enrolling people with type 1 and type 2 diabetes[2,5].

Closed-loop insulin delivery is an emerging therapeutic modality that titrates insulin in response to sensor glucose levels and has been shown to improve glucose control across populations and ages of subjects with type 1 to type 2 diabetes[6-10]. In a post-hoc analysis of an outpatient hybrid closed-loop study, a shorter time to peak to insulin levels was associated with improved glucose control[11] supporting the general notion that faster insulin absorption such as that presented by faster insulin aspart due to its more favourable pharmacokinetic profile can further improve the performance of closed-loop systems. The objective of this pilot study was to evaluate whether short-term use of fully closed-loop insulin delivery using faster versus standard insulin aspart in insulin-treated adults with type 2 diabetes improves glucose control.

RESEARCH DESIGN AND METHODS

Study design and procedures

This was a randomized, single-centre, double-blind, two-period, crossover study in 15 adults with insulin-treated type 2 diabetes. The protocol was approved by the local Ethics Committee and Swissmedic, and conducted from April 10, 2018 to September 9, 2018 in accordance with Good Clinical Practice Guidelines and the Declaration of Helsinki. All participants gave written informed consent prior to commencing study procedures.

Participants were recruited from the outpatient diabetes clinic at University Hospital Bern. Inclusion criteria were age≥18years, type 2 diabetes treated with basal-bolus insulin for ≥3months, and haemoglobin A1c≤11.0% (97mmol/mol). Exclusion criteria were type 1 diabetes, pregnancy or breastfeeding, and incapacity to give informed consent or follow study procedures.

Participants were assigned to receive either faster insulin aspart followed by standard insulin aspart, or vice versa, using computer generated block randomisation (1:1). They attended the study centre at 1830 for 22hours (Figure S1, Supplemental Appendix) twice, separated by a 1-2 week washout, and on each occasion underwent identical procedures. The Freestyle Navigator II continuous glucose monitor (Abbott Diabetes Care, Alameda, CA, USA) was inserted 1-4 days before each visit. Long-acting insulin dose was halved if injected in the morning or withheld if injected in the evening prior to

study visits. All non-insulin agents were continued except for sulphonylurea medication. After arrival, a cannula was inserted in the abdomen for subcutaneous insulin delivery (Fiasp or Novorapid, Novo Nordisk, Bagsvaerd, Denmark) by a study pump (Dana R Diabecare, Sooil, Seoul, South Korea). The closed-loop algorithm comprised a model predictive controller (version 0.3.70) residing on a tablet device (Dell Latitude 10 Tablet, Dell, TX, USA) linked by USB to the continuous glucose receiver and by Bluetooth to the pump (Figure S2). We initialized the system using the participant's weight and total daily insulin dose, which were kept identical for both visits. The algorithm did not account for background basal insulin and no adaptation was made to factor in the pharmacokinetic differences of the two insulin formulations. Closed-loop glucose control without announcement or bolusing for meals was started and continued until 1700 the next day.

After start of closed-loop, participants were served a sandwich and went to bed afterward. The next morning, a peripheral intravenous cannula was inserted for regular plasma glucose sampling every 15min from 0700-1000 and 1200-1500, every 30min from 1000-1200 and 1500-1700, using the Biosen C-Line Analyser (EKF Diagnostics, Barleben, Germany). Standardized meals were consumed at 0700 (53.7±8.8g carbohydrates) and 1200 (72.8±17.5g carbohydrates), matched on both study visits. Decaffeinated sugar-free tea or water were served *ad libitum* during the test. Subjects remained largely sedentary during visits except for a 20min-walk 3h after breakfast. Participant's insulin therapy was resumed at the end of the study visit before discharge.

Study outcomes and statistical analysis

Participants and the study staff were blind to the study treatment until after the final data analysis. Due to the pilot nature of the study, no formal power calculation was applied. We aimed to analyse 15 participants with complete data. The primary endpoint was the percentage of time with plasma glucose between 5.6 to 10.0mmol/l from 0700 to 1700 (10h), in line with previous studies in adults with type 2 diabetes using the same fully closed-loop insulin delivery system[12,13]. Other endpoints are listed in Table S1. Treatments were compared using linear mixed-effect models with treatment as fixed, and period and subject as random effects. P-values<0.05 (two-sided) were considered statistically significant. Statistical analyses were performed using SPSS, Version 23 (IBM Software, Hampshire, UK).

RESULTS

Out of 26 invitees, 20 consented and 15 were included in the analysis (Figure S3). Baseline characteristics and diabetes therapy are summarized in Table S2 and Table S3.

Primary and secondary endpoints are shown in Table 1. The proportion of time with plasma glucose in target range did not differ between the treatments (67.7±16.3 vs. 70.9±17.3%, mean difference [95%CI] -3.3% [-8.2;1.7], p=0.17). Mean glucose and glucose variability were comparable as was time spent below and above target. The 2h-postprandial glucose increment was not different after breakfast (p=0.78) but was significantly higher after lunch with faster insulin aspart (p=0.047). Sensor-

based outcomes over the 10h study period and secondary outcomes over the entire study period are shown in Table S4 and Table S5. Insulin dose was significantly higher with faster insulin aspart (31.9±22.6 vs. 28.2±20.1U, mean difference [95%CI] 3.7U [0.7;6.8], p=0.021). Glucose and insulin delivery profiles are illustrated in Figure 1. One hypoglycaemic event (plasma glucose<3.5mmol/l) occurred with faster insulin aspart and two with standard insulin aspart, which were treated with 15g of rapid-acting oral carbohydrates as per protocol, without the need for intravenous dextrose. Hypoglycaemic events occurred in the late postprandial period before lunch in all participants. One subject experienced twice capillary blood glucose level>20mmol/l without ketonemia after dinner. No severe hypoglycaemia or other serious adverse events occurred (Table S6).

CONCLUSIONS

The present pilot study demonstrated that short-term fully automated-closed loop in type 2 diabetes using faster and standard insulin aspart resulted in comparable glucose control but required higher dose of faster insulin aspart to achieve such outcomes. No differences in hypoglycaemia were observed.

To our knowledge, this is the first study assessing the incremental benefit of faster insulin aspart during short-term use of fully closed-loop insulin delivery in type 2 diabetes. Previous trials that evaluated the use of faster versus standard insulin aspart with injection and pump therapy reported no significant differences for overall glycaemic control between the two insulin formulations[14-18]. Several factors may explain the lack of improved glucose control during short-term application of fully closed-loop despite the more favourable pharmacokinetic and pharmacodynamic profile of faster insulin aspart[2] that has also recently been confirmed in adults with type 2 diabetes[5]. First, the adaptation of the fully closed-loop control algorithm to higher insulin doses needed with faster insulin aspart, which may in part be related to the left-shift of the pharmacokinetic profile, may take longer and the short study duration was not permissive for this to happen. Second, the difference in the onset of action, 8.9min earlier[5], is modest, especially in the light of the considerable intra-patient variability in insulin absorption[19], thereby diminishing potential benefits. Thus, further longer and adequately powered studies are warranted.

The previously reported superior postprandial glucose control of faster insulin aspart compared to standard insulin aspart when administered as a meal bolus during pump or injection therapy in type 1 and type 2 diabetes[14,16,18] does not concur with our findings. We observed postprandial glycaemic increments that were comparable after breakfast and even higher with faster insulin aspart after lunch. The dynamic setting of fully closed-loop, without administration of predetermined meal bolus, may have accounted for the distinct findings. Hybrid closed-loop which applies meal announcement or bolus delivery is more comparable with conventional pump or injection therapy than fully closed-loop in terms of postprandial glucose control. Further studies are required to elucidate the role of faster insulin aspart for meal-time glucose control during fully and hybrid closed-loop control and dissect the

causes of the discord between our findings observed during fully closed-loop glucose control versus those observed during conventional pump or injection therapy.

The occurrence of hypoglycaemia did not differ between the two treatments. All hypoglycaemic events occurred in participants treated with insulin degludec. Residual background long-acting insulin levels could have been contributory as these were not accounted for during initialization of closed-loop. Thus, consideration of exposure to background insulin may be warranted in patients being treated with ultra-long acting insulin.

The strengths of our study include the novelty of the research question, the double-blind randomized crossover design and the standardized setting. Limitations include the short study duration, small sample size, and a single-centre study design. Findings of the present pilot study may inform the design of future studies assessing the performance of closed-loop glucose control using different insulin formulations.

In conclusion, short-term fully automated closed-loop insulin delivery using faster insulin aspart in adults with type 2 diabetes achieved comparable glucose control with a higher insulin dose compared to standard insulin aspart. Further research is needed to assess the benefits of faster insulin aspart for closed-loop insulin therapy in different populations.

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Conflicts of interest

CS reports having received speaker honoraria from Medtronic and Ypsomed, serving on advisory panels for Novo Nordisk, Medtronic, Roche and Sanofi. RH reports having received speaker honoraria from Eli Lilly and Novo Nordisk, serving on advisory panel for Eli Lilly and Novo Nordisk, receiving license fees from BBraun and Medtronic. RH and MEW report patent applications. LB, DH, YR, MS, MMW, AV and BV declare no competing financial interests.

Author contributions

LB screened and enrolled participants, arranged informed consent from the participants and conducted study visits. LB and AV provided patient care. LB and RH designed the study. LB, DH, YR, MEW and RH performed or supported data analyses. RH designed and implemented the glucose controller. LB, DH and RH interpreted the results and wrote the manuscript. All authors critically reviewed the manuscript. LB and RH are the guarantors of this work and take responsibility for the integrity of the data and the accuracy of the data analysis.

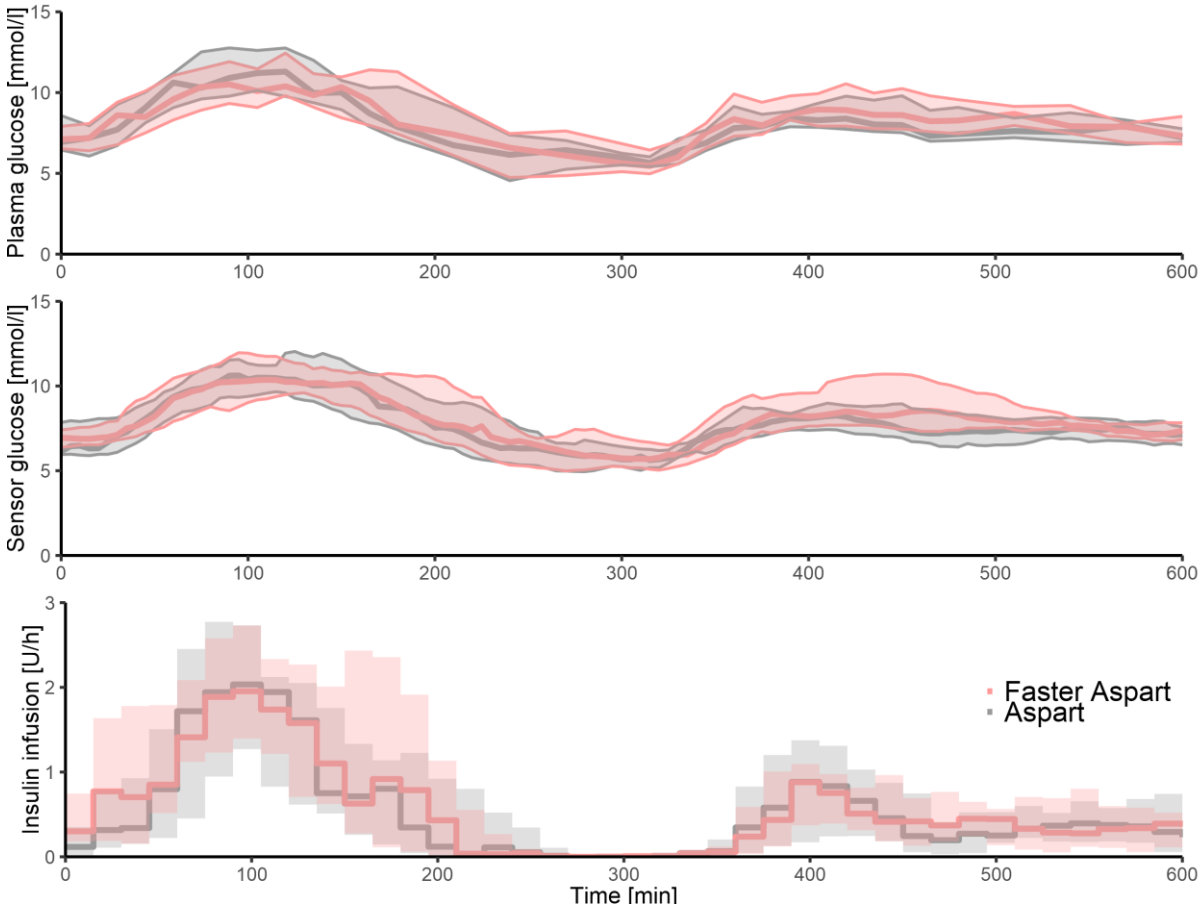
Table 1. Performance of fully closed-loop insulin delivery using faster insulin aspart (FA) and standard insulin aspart (A) over the 10h-period (from breakfast at 0700 to discharge at 1700) based on plasma glucose.

	Closed-loop with FA (n=15)	Closed-loop with A (n=15)	Paired difference* or paired ratio† (FA-A) [95% CI] (n=15)	p value
Time spent at glucose levels (%)				
5.6 to 10.0 mmol/l	67.7±16.3	70.9±17.3	-3.3 [-8.2;1.7]	0.17
>10.0 mmol/l	22.1±18.2	20.3±15.9	1.8 [-4.2;7.8]	0.53
<5.6 mmol/l	10.3±13.4	8.8±11.2	1.5 [-2.0;5.1]	0.37
<3.9 mmol/l	0.0 (0.0-0.0)	0.0 (0.0-5.2)	0.62 [0.37;1.05]†	0.072
Mean glucose (mmol/l)	8.5±1.3	8.3±1.0	0.2 [-0.2;0.6]	0.38
Standard deviation of glucose (mmol/l)	2.0±0.7	2.0±0.7	-0.1 [-0.4;0.3]	0.69
Coefficient of variation of glucose (%)	23.0±8.6	24.5±8.6	-1.5 [-4.0;1.0]	0.22
Hypoglycaemic events (<3.5 mmol/l)	1 [7]	2 [13]	-	1.00
2h breakfast glucose increment (mmol/l)	3.8±1.6	3.9±2.2	-0.1 [-0.9;0.8]	0.78
2h breakfast insulin dose (U)	13.4±11.0	11.8±8.6	1.6 [-0.8;4.0]	0.18
2h lunch glucose increment (mmol/l)	3.7±3.2	2.8±2.6	0.8 [0.0;1.6]	0.047
2h lunch insulin dose (U)	3.7±2.6	3.2±2.3	0.5 [-1.4;2.5]	0.56
10h insulin dose (U)	31.9±22.6	28.2±20.1	3.7 [0.7;6.8]	0.021

Data are mean±SD, median (IQR), mean [95% CI] or n [%]. 2h glucose increment, rise in glucose concentration from start of the meal until two hours later; 2h insulin dose, amount of insulin infused from start of the meal until two hours later. 10h insulin dose, amount of insulin delivered by the fully closed-loop system over the 10hour period. *Unless specified otherwise, data are normally distributed and presented as mean difference of closed-loop with FA minus closed-loop with A, with 95% CI for mean; a positive value indicates that the measurement was higher in the closed-loop period with FA than in the closed-loop period with A. †Non-normally distributed data are presented as ratio of closed-loop with FA data over closed-loop with A data, with 95% CI for ratio; a value greater than unity indicates that the measurement was higher in the closed-loop period with FA than in the closed-loop period with A.

Figure caption

Figure 1. (Panel A) Plasma glucose and (Panel B) sensor glucose concentration during fully closed-loop insulin delivery with faster insulin aspart (red) and standard insulin aspart (grey) (lines indicate median, shaded areas indicate interquartile ranges). (Panel C) Algorithm-directed insulin delivery (line indicates median, shaded area indicates interquartile ranges). Time origin represents breakfast time. **N=15.**



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